NOVARTIS

Regulatory Affairs

NEVANAC®

(nepafenac)

1 mg/mL Eye Drops, suspension

International Package Leaflet

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NEVANAC®

Anti-inflammatory agents, non-steroids.

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Eye drops, suspension.

Light yellow to light orange uniform suspension, pH 7.4 (approximately).

Active substance(s)

1 mL of suspension contains 1 mg nepafenac.

Excipients

Excipient with known effect: 1 mL of the eye drop suspension contains 0.05 mg of benzalkonium choride.

Other excipients: mannitol (E421), carbomer 974P, sodium chloride, tyloxapol, disodium edetate, sodium hydroxide and/or hydrochloric acid (for pH adjustment) and purified water.

INDICATIONS

Nevanac is indicated in adults for:

Prevention and treatment of pain and inflammation associated with cataract surgery.

Reduction in risk of postoperative macular edema associated with cataract surgery in diabetic patients.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

Nevanac 1 mg/mL Eye drops, suspension

For pain and inflammation associated with cataract surgery:

- The dose is 1 drop of Nevanac in the affected eye(s) 3 times daily beginning 1 day prior to cataract surgery and continuing on the day of surgery through the first 2 weeks (14 days) of the postoperative period.
- An additional drop should be administered 30 to 120 minutes prior to surgery.
- Treatment can be extended up to the first 3 weeks (21 days) of the postoperative period, as directed by the clinician.

For reduction in risk of macular edema associated with cataract surgery in diabetic patients:

- The dose is 1 drop of Nevanac in the affected eye(s) 3 times daily. Dosing begins 1 day prior to surgery, continues on the day of surgery and up to 60 days of the postoperative period.
- An additional drop should be administered 30 to 120 minutes prior to surgery.

General target population

- Adults.

Special populations

Renal and hepatic impairment

- Nevanac have not been studied in patients with hepatic disease or renal impairment.
- No dosage regimen adjustment is warranted in these patients, as the systemic exposure is very low following topical ocular administration.

Pediatric patients (below 18 years)

The safety and efficacy of Nevanac in pediatric patients have not been established. Its use is not recommended in this age group until further data become available.

Geriatric patients (65 years of age or above)

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Method of administration

- For ocular use.
- After cap is removed, if tamper evident snap collar is loose, it should be removed before using the product.
- If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.
- If a dose is missed, a single drop should be applied as soon as possible before reverting to regular routine. No double dose should be used to make up for the one missed.
- Shake the bottle well before use.
- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. Patients should be instructed to keep the bottle tightly closed when not in use.

CONTRAINDICATIONS

Hypersensitivity to the active substance, to any of the excipients, or to other non-steroidal anti-inflammatory drugs (NSAIDs).

WARNINGS AND PRECAUTIONS

- Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued and prolonged use may increase patient risk for occurrence and severity of corneal adverse reactions which may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. Post-marketing experience with topical NSAIDs suggests that patients with repeat and/or complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases, dry eye or rheumatoid arthritis may be at increased risk for corneal adverse reactions. These events may be sight threatening. Topical NSAIDs should be used with caution in these patients. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of Nevanac and should be monitored closely for corneal health.

- Topical NSAIDs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Nevanac should be used with caution in patients with known bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time.
- There is a potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory agents.

Special excipients

- Nevanac Eye drops, suspension contains benzalkonium chloride which may cause eye irritation and may possibly discolor soft contact lenses. Contact lenses must be removed before administration of Nevanac Eye drops, suspension and reinserted at least 15 minutes later.
- Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent and/or prolonged use.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

System organ classification	Adverse drug reaction	Frequency category
Nervous system disorders	Dizziness, headache	Rare
Eye disorders	Keratitis, punctate keratitis, corneal epithelium defect, conjunctivitis allergic, eye pain, foreign body sensation in eyes, eyelid margin crusting	Uncommon
	Blurred vision, photophobia, dry eye, blepharitis, eye irritation, eye pruritus, eye discharge, lacrimation increased	Rare
Immune system disorders	Hypersensitivity	Rare
Gastrointestinal disorders	Nausea	Rare
Skin and subcutaneous tissue disorders	Allergic dermatitis	Rare

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Nevanac via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System organ classification	Adverse drug reaction
Eye disorders	Corneal perforation, ulcerative keratitis, corneal thinning, corneal opacity, corneal scar, impaired healing (cornea), visual acuity reduced, eye swelling, ocular hyperaemia
Gastrointestinal disorders	Vomiting
Investigations	Blood pressure increased

INTERACTIONS

Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Concomitant use of Nevanac with medications that prolong bleeding time may increase the risk of hemorrhage (see section WARNINGS AND PRECAUTIONS).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. There are limited data with the use of Nevanac in pregnant women.

In embryofetal studies in rats and rabbits, oral administration of nepafenac during the period of organogenesis did not produce embryofetal toxicity at 10 mg/kg/day (20 times and 179 times higher than human exposures based on AUC of nepafenac and amfenac at the maximum recommended ocular human dose (MROHD) of one drop of 0.3 % nepafenac ophthalmic suspension in each eye, respectively).

Oral administration of nepafenac to pregnant rats during gestation and lactation produced maternal lethality at all doses, including the lowest dose tested, 3 mg/kg/day.

A no-observed effect-level (NOEL) for maternal toxicity was not established in this study. Doses ≥3 mg/kg/day were associated with dystocia and doses ≥10 mg/kg/day increased the death rate of the offspring, especially during the early neonatal period.

Since human systemic exposure is negligible (<1ng/mL) after treatment with Nevanac, the risk during pregnancy could be considered low. Nevertheless, inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryofetal development and/or parturition and/or postnatal development.

Pregnant women should be advised of a potential risk to the fetus. Nevanac should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Clinical considerations

Fetal/Neonatal adverse reactions

Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of Nevanac during late pregnancy should be avoided.

Data

Animal data

In rats, oral administration of 3, 10 or 30 mg/kg/day nepafenac during the period of organogenesis (gestational days 6 to 17) caused significant maternal toxicity at 10 mg/kg/day and maternal lethality at 30 mg/kg/day. The NOEL for maternal toxicity was 3 mg/kg/day (17 and 351 times higher than human exposure to nepafenac and amfenac at MROHD, respectively. A dose of 30 mg/kg/day produced embryofetal toxicity (embryofetal lethality and increased incidence of minor skeletal anomalies). The NOEL for embryofetal toxicity was 10 mg/kg/day (212 and 1,432 times higher than human exposure to nepafenac and amfenac at MROHD, respectively).

In rabbits, oral administration of 3, 10 or 30 mg/kg/day nepafenac during the period of organogenesis (gestational days 6 to 18) caused abortion at ≥10 mg/kg/day. The NOEL for abortion and maternal toxicity was 3 mg/kg/day (0.6 and 41 times higher than human exposure to nepafenac and amfenac at MROHD, respectively). Embryofetal toxicity, including external, visceral and skeletal malformations (omphalocele, malformations of the heart/great vessels; and skull, vertebrae, sternebrae and costal cartilage anomalies) was produced at 30 mg/kg/day. The NOEL for embryofetal toxicity was 10 mg/kg/day (20 and 179 times higher than human exposure to nepafenac and amfenac at MROHD, respectively).

In a peri- and postnatal study in rats, oral administration of 3, 10, 15 or 30 mg/kg/day nepafenac during organogenesis and through lactation (gestational days 6 through lactation day 20) caused treatment-related maternal lethality at all doses, with deaths generally following initiation of parturition. A NOEL for maternal toxicity was not established in this study. Maternally toxic doses ≥3 mg/kg/day were associated with dystocia, while doses ≥10 mg/kg/day increased post-implantation loss, reduced fetal growth/weight, and reduced fetal survival. At 15 mg/kg/day, pup viability continued to decrease during the first four days of lactation. No further spontaneous pup mortality occurred after lactation day 4. Nepafenac caused no developmental toxicity in surviving F1 offspring and did not elicit adverse effects with respect to F1 reproductive parameters or F2 viability and growth. The NOEL for developmental toxicity was 3 mg/kg/day (17 and 351 times higher than human exposure to nepafenac and amfenac at MROHD, respectively).

Lactation

Risk summary

There is no information regarding the presence of nepafenac in human milk, the effects on breast-fed infants, or on milk production. Nepafenac is transferred into the milk of lactating rats

after oral administration with a milk to plasma ratio of <0.6. It is not known whether measurable levels of nepafenac would be present in maternal milk following topical ocular administration.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Nevanac and any potential adverse effects on the breast-fed child from Nevanac.

Females and males of reproductive potential

Infertility

There are no adequate data regarding the use of Nevanac on human fertility. No significant fertility effects were seen in studies in rats at doses up to 3 mg/kg/day (17 and 351 times higher than the human exposure to nepafenac and amfenac at the MROHD, respectively).

In a fertility study, rats were orally dosed with 3, 10, 15 and 30 mg/kg/day. Animals at 30 mg/kg/day were euthanized early due to excessive toxicity. At 15 mg/kg/day, sperm motility and concentration were affected in males in the absence of any microscopic findings in the testes and epididymides. No significant differences in copulation or fertility indices were noted. Decreased number of viable fetuses and increased early resorptions were observed at 10 and 15 mg/kg/day. The NOEL for male and female reproductive toxicity was 3 mg/kg/day (17 and 351 times higher than the human exposure to nepafenac and amfenac at the MROHD, respectively).

OVERDOSAGE

No toxic effects are likely to occur in case of overdose with ocular use, nor in the event of accidental oral ingestion.

CLINICAL PHARMACOLOGY

Pharmacodynamic Properties

Mechanism of action (MOA)

Nepafenac is a non-steroidal anti-inflammatory and analgesic pro-drug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular hydrolases to amfenac, a non-steroidal anti-inflammatory drug. Amfenac inhibits the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

Pharmacodynamics (PD)

The majority of hydrolytic conversion is in the retina/choroid followed by the iris/ciliary body and cornea, consistent with the degree of vascularized tissue. No significant effect on intraocular pressure has been reported in clinical trials.

Pharmacokinetics (PK)

Absorption

Following 3 time daily dosing of Nepafenac 0.1 % Eye drops in both eyes for four days, maximal steady-state plasma concentrations (Cmax) of nepafenac (0.310 + 0.104 ng/mL) and amfenac (0.422 + 0.121 ng/mL) were attained within 0.5 hours. Steady-state plasma levels were achieved by day 2. The mean nepafenac and amfenac AUC0-∞ were 0.371 ng·h/mL and 1.03

ng·h/mL, respectively. Based on the steady-state/single dose ratio of individual Cmax values, the mean accumulation index was 1.34 + 0.58 for nepafenac and 1.61 + 0.66 for amfenac.

For nepafenac 0.3% suspension, once daily dosing in both eyes after four days produced Cmax of 0.847 ng/mL for nepafenac and 1.13ng/mL for amfenac, which was attained at 0.5 hours. The mean nepafenac and amfenac AUC0-∞ were 1.43 ng·h/mL and 3.70 ng·h/mL, respectively. The half-life for amfenac was approximately 5-fold longer in plasma than for nepafenac. The steady-state/single dose mean accumulation ratio was ≈ 1; therefore, no accumulation was observed for either nepafenac or amfenac after ocular dosing with 0.3% suspensionion.

Distribution

Nepafenac and amfenac distributed to ocular tissues in rabbits after single topical dose with either 0.1% or 0.3% suspension. Higher concentrations were observed at site of dosing, cornea and conjunctiva and lower concentrations in posterior tissues, retina and choroid. Concentrations in ocular tissues increased with increased dose. When anterior ocular tissues concentrations were compared from a single dose of 0.3% nepafenac to that after three doses of 0.1% nepafenac in a single day, only the lens did not have a higher concentrations after the 0.3% nepafenac once a day dosing.

In cataract surgical patients, maximal aqueous humor concentrations were observed 1 hour following single dose of 0.1% nepafenac with a concentration of 177 ng/mL and 44.8 ng/mL for nepafenac and amfenac, respectively.

Plasma protein binding of nepafenac is moderate, ranging from 72.8% in rat plasma to 83.5% in human plasma. Protein binding was found to be concentration independent in rat, monkey and human plasma over a wide concentration range (10 to 1,000 ng/mL). Amfenac is more highly bound at approximately 99%.

Biotransformation/metabolism

Nepafenac undergoes relatively rapid in vivo hydrolysis to amfenac. After oral administration, unconjugated amfenac and nepafenac, and eight other metabolites were detected in plasma with amfenac, a pharmacological active metabolite having the highest concentration. Several of the metabolites were glucuronide conjugates based chromatographic shift after beta-glucuronidase treatment. Nepafenac was detected in plasma but at relatively low levels (3.2% of total radioactivity). Amfenac was the major metabolite in plasma, representing approximately 13% of total plasma radioactivity. The second most abundant plasma metabolite was 5-hydroxy nepafenac in the form of a glucuronide, representing approximately 9.5% of total radioactivity at Cmax.

Neither nepafenac nor amfenac inhibit any of the major human cytochrome P-450 isozymes (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) in vitro at concentrations up to 3,000 and 1,000 ng/mL, respectively.

After 14 days of oral administration, nepafenac does not increase CYP1A, CYP2B, CYP3A activities or total P450 content in rat, therefore no potential induction was observed for rat.

Elimination

After oral administration of 14C-nepafenac to healthy human volunteers, urinary excretion was found to be the major route of excreted radioactivity, accounting for approximately 85% while fecal represented approximately 6% of the dose out to 7 days.

CLINICAL STUDIES

Nevanac is a well established product.

NON-CLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based upon conventional studies of single dose toxicity, repeated dose toxicity, genotoxicity and topical ocular irritation studies. Nepafenac has not been evaluated in long-term carcinogenicity studies.

For information on reproductive and developmental toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

None known.

STORAGE

See folding box.

Nevanac should not be used after the date marked “EXP” on the pack.

Nevanac must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

Manufacturer:

See folding box.

International Package Leaflet

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Novartis Pharma AG, Basel, Switzerland